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Excessive Atrial Ectopy and Short Atrial Runs Increase the Risk of Stroke Beyond Incident Atrial Fibrillation

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CME Objective for This Article: After reading this article, the reader should be able to: 1) identify cardiovascular risk factors associated with high-grade atrial ectopy; 2) discuss the relationship between clinical risk factors and development of ischemic stroke; 3) discuss the clinical significance of increasing high-grade atrial ectopy (excessive atrial ectopy) in relation to atrial fibrillation and ischemic stroke (linear and nonlinear associations); 4) discuss in which populations or groups excessive number of premature atrial contractions (PACs) has shown to be associated with an increased risk of stroke and how large the magnitude of risk is compared to similar patients with atrial fibrillation; 5) explain how recent studies have defined "excessive atrial ectopy"; and 6) discuss whether there are any guideline-recommended therapies with respect to excessive atrial ectopy.

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Excessive Atrial Ectopy and Short Atrial Runs Increase the Risk of Stroke Beyond Incident Atrial Fibrillation

ABSTRACT

BACKGROUND Approximately 30% of ischemic strokes have an unknown cause. Increased atrial ectopy (AE) increases the risk of atrial fibrillation (AF), but the risk of stroke in patients with increased AE is unknown.

OBJECTIVES This study aimed to examine whether increased AE and short atrial runs increase the risk of stroke beyond incident AF.

METHODS Data were collected during a 15-year follow-up of the Copenhagen Holter Study cohort with 678 men and women between 55 and 75 years of age, with no earlier history of cardiovascular disease, stroke, or AF. Study subjects underwent 48-h ambulatory electrocardiography, fasting blood tests, and clinical examination. Excessive supraventricular ectopic activity (ESVEA) was defined as the presence of either ≥30 premature atrial contractions (PACs)/hour daily or any runs of ≥20 PACs.

RESULTS Ninety-nine subjects (15%) demonstrated ESVEA. After adjusting for baseline risk factors, ESVEA was associated with ischemic stroke when censoring subjects at time of AF (hazard ratio [HR]: 1.96; 95% confidence interval [CI]: 1.10 to 3.49) or when modeling AF as a time-varying exposure (HR: 2.00; 95% CI: 1.16 to 3.45). Among subjects with ESVEA who developed a stroke, 14.3% had diagnosed AF before their stroke. The incidence of stroke in subjects with ESVEA and a CHA_2DS_2-VASc (congestive heart failure, hypertension, age 75 years or older, diabetes mellitus, previous stroke or transient ischemic attack, vascular disease, age 65 to 74 years, female) score of ≥2 was 2.4% per year, comparable to the risk observed in AF. In day-to-day analysis, ESVEA was a consistent finding.

CONCLUSIONS ESVEA was associated with an increased risk of ischemic stroke beyond manifest AF in this middle-aged and older population. Stroke was more often the first clinical presentation, rather than AF, in these study subjects. (J Am Coll Cardiol 2015;66:232–41) © 2015 by the American College of Cardiology Foundation.

Despite meticulous research for the etiology of ischemic stroke, 25% to 30% of strokes remain unexplained and are consequently labelled cryptogenic (1,2). Occult atrial fibrillation (AF) is thought to be partly responsible for this phenomenon (3–9). However, paroxysmal AF often goes undetected as a result of the heterogeneous presentation with no symptoms, a short duration, and episodic runs (10). This issue has prompted new strategies to detect incident AF, especially through prolonged electrocardiogram (ECG) monitoring (3–9). In recent years increased atrial ectopy (AE) has been shown to be associated with a higher risk of AF (11–15). Some studies have reported an association with stroke as well, but the increased risk is thought to be secondary to subsequent AF (11,12). The risk of stroke in persons with increased AE is unknown, and it is also not known whether these persons will present with clinical AF before having a stroke. This study investigated the independent association between increased AE and ischemic stroke.

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We hypothesized that excessive supraventricular ectopic activity (ESVEA) independently increases the risk of ischemic stroke, comparable to AF.

METHODS

COPENHAGEN HOLTER STUDY. The Copenhagen Holter Study included patients enrolled between April 1998 and June 2000. Follow-up was performed in 2013, thus including up to 15-years of follow-up in some patients. The aim of the follow-up study was to address the value of 48-h Holter recording in relation to other risk factors, in the assessment of future adverse events in terms of AF, ischemic stroke, and mortality in middle-aged and older men and women. Information about the study protocol and the selection procedures

ABBREVIATIONS AND ACRONYMS

AE = atrial ectopy

AF = atrial fibrillation

CHA_2DS_2-VASc = congestive heart failure, hypertension, age 75 years or older, diabetes mellitus, previous stroke or transient ischemic attack, vascular disease, age 65 to 74 years, female

ECG = electrocardiogram

ESVEA = excessive supraventricular ectopic activity

NT-proBNP = N-terminal prohormone of brain natriuretic peptide

PAC = premature atrial contraction

were published previously (16). Briefly, all men 55 years and all men and women 60, 65, 70, and 75 years of age (n = 2,969) who were living within 2 defined postal regions in the city of Copenhagen were contacted with a questionnaire regarding cardiovascular risk factors, medication use, and medical history. All responding individuals with >1 risk factor, and 60% of randomly selected subjects with 0 to 1 risk factors were invited to follow-up consisting of a physician-based questionnaire, physical examination, laboratory testing, ECG and 48-h continuous ECG recording. Subjects with current or past AF, manifest ischemic heart disease, congestive heart failure, valvular heart disease, congenital heart disease, angina pectoris, stroke, cancer, or other life-threatening conditions were excluded. This resulted in 678 participants who underwent fasting laboratory tests, a physical examination with anthropometric measurements, and up to 48 h of continuous Holter monitoring. Holter recording was performed with the use of 2-channel SpaceLabs tape recorders (9025, SpaceLabs, Inc., Redwood, Washington). Recordings were evaluated and interpreted by trained personnel, and the interobserver variability shows kappa values between 0.91 and 0.94 (17). Median value of technically acceptable recording was 44.1 h, and first and third quartiles (Q1, Q3) were 41.4 to 45.5 h; 98% of the subjects had >24 h of recording.

DEFINITIONS. In accordance with previous definitions (11), 2 classes of supraventricular arrhythmias were investigated: premature atrial contractions (PACs) and runs of ≥3 PACs. The basis of verification of PAC consisted of 3 criteria: prematurity, post-contraction pause, and morphology. The coupling interval to the preceding QRS complex had to be ≤70% of the mean RR interval of basic rhythm before the event. QRS complexes had a length of <0.11 s unless aberration was assumed. The post-contraction pause had to be noncompensatory. Frequency of PACs and length of runs of PACs were analyzed as both continuous and dichotomized variables. Assuming that PACs had to be excessive to increase adverse events, the cutoff value was set at the top decile in both frequency of PACs and length of runs of PACs. Accordingly, ESVEA was defined as ≥30 PACs/h or any episode of runs of ≥20 PACs.

FOLLOW-UP. Events of stroke, incident AF, and death were retrieved from the national central patient registry and from discharge letters and were validated by reviewing patients' files. The diagnosis of stroke was made on the basis of clinical findings with a confirmed diagnosis by computed tomography or magnetic resonance imaging. All nonischemic strokes were excluded in the analysis for this paper. The diagnosis of incident AF was verified with documentation in the form of ECG, telemetry, or both, from patient records. All medications were registered at baseline, and no participants were receiving treatment with anticoagulants. Endpoints included were stroke and a combined endpoint of all-cause mortality or first event of stroke.

ETHICS. All participants provided written informed consent. The regional ethical committee of Copenhagen and Frederiksberg approved the study. The study is in compliance with the Helsinki Declaration.

STATISTICAL ANALYSIS. Mean ± SD is reported for continuous variables with a normal distribution. Data that are not normally distributed are presented as median with interquartile ranges. Pearson chi-square test, Fisher exact test, 2-tailed Student *t* test, and Wilcoxon rank-sum test (Mann-Whitney *U* test) were used for the comparison of groups as appropriate. Kaplan-Meier survival function was used to compare event-free survival in different groups according to ESVEA, and the log rank test (Mantel-Cox test) was used to test for equality of the survivor function.

Cox proportional hazards model estimated the hazard of ESVEA in relation to the endpoint of stroke, or the composite endpoint of death or stroke. To estimate the effect of incident AF on our primary endpoints, we used a Cox regression model with censoring at time of AF and another model with AF as a time-varying exposure. Furthermore, the association between ESVEA and stroke was assessed using the competing risk proportional subhazard model by the method of Fine and Gray (18), in which AF and "dead" were modeled as competing risks to the endpoint of stroke. The selection of potentially confounding covariates in Cox regression models and competing risk models was made on the basis of existing knowledge about their relationship with ischemic stroke and by risk factors associated with ischemic stroke at baseline. In further exploration of the data, we added ESVEA to a Cox proportional hazard model with the Framingham Stroke Risk Score (19) as a continuous variable. Improvement of the model with entrance of ESVEA was assessed by a likelihood ratio test.

The assumption of linearity for continuous covariates was tested and confirmed. The proportional hazard assumption was tested for each of the Cox models on the basis of Schoenfeld residuals. To evaluate the stability of ESVEA, we calculated kappa values of having >30 PACs/h on 2 separate days. Data on the daily variation of PACs were available for analysis in

644 subjects (95% of the population). Any 2-tailed p value <0.05 was considered significant. Statistical analysis was performed using STATA version 13.0 (StataCorp, College Station, Texas).

RESULTS

STUDY POPULATION. A total of 678 patients participated in this study. Median follow-up was 14.4 years, and no patients were lost to follow-up. The baseline characteristics of the population with and without stroke in the follow-up and ESVEA at baseline are shown in Table 1. Subjects who had a stroke were likely to be older, smokers, with higher blood pressure, a higher CHA_2DS_2-VASc (congestive heart failure, hypertension, age 75 years or older, diabetes mellitus, previous stroke or transient ischemic attack, vascular disease, age 65 to 74 years, female) score, and higher N-terminal prohormone of brain natriuretic peptide (NT-proBNP) levels, and they were more prone to be taking antithrombotic medication. Ninety-nine subjects were classified as having ESVEA; 70 subjects had >30 PACs/h daily, and 42 had runs of PACs with a length greater than ≥20 PACs. Thirteen subjects had both irregularities. Study subjects with ESVEA at baseline shared many of the same baseline risk factors as subjects who later developed ischemic stroke.

FOLLOW-UP AND ENDPOINTS. Ischemic stroke occurred in 73 subjects, of whom 21 (29%) had ESVEA at baseline. Subjects with ESVEA had 21.5 strokes/1,000 person-years, and subjects without ESVEA had 7.4 strokes/1,000 person-years (hazard ratio [HR]: 2.07; 95% confidence interval [CI]: 1.21 to 3.56) after adjustment for age, sex, smoking, total cholesterol, diabetes, body mass index, and systolic blood pressure. Further adjustments for aspirin use and NT-proBNP did not affect the results significantly (HR: 2.02; 95% CI: 1.17 to 3.49). A total of 259 subjects died in the follow-up period, and 287 subjects had a combined outcome of death or stroke: 58.5 events/1,000 person-years in subjects with ESVEA, and 32.7 events/1,000

TABLE 1 Cardiovascular Risk Factors of the Study Population Stratified by the Occurrence of Ischemic Stroke and ESVEA at Baseline

		Stroke		ESVEA	
	All (n = 678)	No (n = 605)	Yes (n = 73)	No (n = 579)	Yes (n = 99)
Age, yrs	64.5 ± 6.8	64.1 ± 6.8	67.7 ± 6.4*	64.0 ± 6.8	67.6 ± 6.3*
ESVEA	99 (14.6)	78 (12.9)	21 (28.8)*	–	–
Female	281 (41.4)	252 (41.7)	29 (39.7)	246 (42.5)	35 (35.4)
Current smoking	314 (46.3)	272 (45.0)	42 (57.5)†	267 (46.1)	47 (47.5)
Diabetes mellitus	75 (11.1)	63 (10.2)	12 (16.5)	63 (10.9)	12 (12.1)
Glucose, mmol/L	5.8 ± 1.7	5.8 ± 1.7	6.2 ± 2.0	5.8 ± 1.8	5.8 ± 1.1
Systolic blood pressure, mm Hg	156.4 ± 24.2	155.3 ± 24.3	165.5 ± 21.6*	155.4 ± 23.8	162.3 ± 25.7*
Diastolic blood pressure, mm Hg	90.9 ± 10.9	90.6 ± 11.1	93.5 ± 9.5†	90.7 ± 11.1	92.1 ± 10.0
CHA_2DS_2-VASc			*		*
0	141 (20.8)	135 (22.3)	6 (8.2)	131 (22.6)	10 (10.1)
1	164 (24.2)	151 (25.0)	13 (17.8)	145 (25.0)	19 (19.2)
2	189 (27.9)	163 (26.9)	26 (35.6)	155 (26.8)	34 (34.3)
≥3	184 (27.1)	156 (25.8)	28 (38.4)	148 (25.6)	36 (36.4)
Total cholesterol, mmol/l	6.0 ± 1.0	6.1 ± 1.1	6.0 ± 1.0	6.1 ± 1.0	5.8 ± 1.0†
LDL-cholesterol, mmol/l	3.9 ± 1.0	3.9 ± 1.0	3.9 ± 0.9	3.9 ± 0.9	3.6 ± 1.0†
NT-proBNP, pmol/l	6.9 (3.6–13.8)	6.5 (3.5–13.0)	8.6 (5.2–21.9)*	6.3 (3.3–12.3)	12.4 (5.5–25.7)*
Log (NT-proBNP)	2.0 ± 1.1	1.9 ± 1.1	2.3 ± 1.1*	1.9 ± 1.1	2.6 ± 1.1*
C-reactive protein, mg/l	2.5 (1.1–4.6)	2.5 (1.1–4.6)	2.7 (1.2–4.6)	2.4 (1.1–4.5)	2.9 (0.9–6.2)
Log (C-reactive protein)	0.9 ± 1.1	0.8 ± 1.1	1.0 ± 1.0	0.8 ± 1.1	1.0 ± 1.2
Alcohol, units/week	13.0 (0–26)	13.0 (0–26)	11.0 (4–27)	13.0 (3–27)	12.0 (0–24)
Low level of physical activity	174 (25.9)	155 (25.8)	19 (26.4)	147 (25.6)	27 (27.6)
Body mass index, kg/m^2	26.8 ± 4.4	26.8 ± 4.3	26.6 ± 4.6	26.7 ± 4.2	27.0 ± 5.2
Aspirin use	103 (15.2)	84 (13.9)	19 (26.0)*	81 (14.0)	22 (22.2)*
β-Blocker use	34 (5.0)	29 (4.8)	5 (6.8)	30 (5.2)	4 (4.0)
Diuretic use	121 (17.8)	102 (16.9)	19 (26.0)	96 (16.6)	25 (25.3)*
ACE inhibitor use	32 (4.7)	26 (3.7)	6 (8.2)	27 (4.7)	5 (5.1)

Values are mean ± SD, n (%), or median (Q1 to Q3). *p < 0.01. †p < 0.05. p values reported are within-group differences. The p value of the CHA_2DS_2-VASc score is a test of overall within-group difference.

ACE = angiotensin-converting enzyme; CHA_2DS_2-VASc = congestive heart failure, hypertension, age 75 years or older, diabetes mellitus, previous stroke or transient ischemic attack, vascular disease, age 65 to 74 years, female; ESVEA = excessive supraventricular ectopic activity; LDL = low-density protein; NT-proBNP = N-terminal prohormone of brain natriuretic peptide.

person-years in subjects without ESVEA (HR: 1.44; 95% CI: 1.06 to 1.95) after adjustment for age, sex, smoking, total cholesterol, diabetes, body mass index, and systolic blood pressure. Further adjustment for aspirin and NT-proBNP did not change the results significantly (HR, 1.38; 95% CI: 1.01 to 1.89). Seventy-seven subjects were diagnosed with incident AF during follow-up, and 18 of these subjects (23%) had ESVEA at baseline.

RISK ASSOCIATED WITH ESVEA BEYOND AF. When censoring subjects at time of AF, ischemic stroke occurred more frequently in subjects with ESVEA than in those without (19.9 vs. 7.2/1,000 patient-years; $p = 0.0001$).

In multivariate Cox models with censoring at time of AF and after adjustment for relevant baseline risk factors, ESVEA was associated with stroke and the combined endpoint of death or stroke (Table 2). ESVEA remained associated with stroke in fully adjusted models when modeling AF as a time-varying exposure; however, the combined endpoint of stroke and death became borderline significant (Table 3). In a Fine-Gray competing risk model with AF and death as competing risks and after adjusting for age and sex, ESVEA remained correlated with stroke (subdistribution hazard: 1.82; 95% CI: 1.03 to 3.22). However, the results attenuated to insignificant (subdistribution hazard: 1.60; 95% CI: 0.87 to 3.22) after adjusting for additional stroke risk factors (age, sex, smoking, total cholesterol, diabetes, body mass index, and systolic blood pressure).

ESTIMATED RISK OF STROKE ASSOCIATED WITH ESVEA. We calculated the absolute risk of stroke according to the subjects' CHA_2DS_2-VASc score at baseline. A stepwise increase in the rates of stroke was observed with increasing score, and a significantly higher risk was seen in the patients with ESVEA, as illustrated in Figure 1 ($p = 0.0002$). Subjects with ESVEA and CHA_2DS_2-VASc score ≥2 had an absolute risk of stroke equal to 2.4% per year.

TABLE 2 Cox Regression Models Showing the Hazard Ratio of ESVEA in Relation to Stroke and Death or Stroke, Where Subjects are Censored at the Time of Atrial Fibrillation

	Stroke	Death or Stroke
ESVEA in Model 1*	2.16 (1.24–3.76) p = 0.007	1.54 (1.14–2.07) p = 0.004
ESVEA in Model 2†	1.96 (1.10–3.49) p = 0.022	1.51 (1.11–2.05) p = 0.008

Values are hazard ratio (95% confidence interval). *Model 1: adjusted for age and sex. †Model 2: adjusted for additional stroke risk factors (age, sex, smoking, total cholesterol, diabetes, body mass index, and systolic blood pressure).
ESVEA = excessive supraventricular ectopic activity.

TABLE 3 Cox Regression Models Showing the Hazard Ratio of ESVEA in Relation to Stroke and Death or Stroke, Where Atrial Fibrillation is Modeled as a Time-Varying Exposure

	Stroke	Death or Stroke
ESVEA in Model 1*	2.28 (1.34–3.88) p = 0.002	1.38 (1.02–1.87) p = 0.036
ESVEA in Model 2†	2.00 (1.16–3.45) p = 0.013	1.35 (0.99–1.84) p = 0.053

Values are hazard ratio (95% confidence interval). *Model 1: adjusted for age, sex, and incident atrial fibrillation. †Model 2: adjusted for additional stroke risk factors (age, sex, incident atrial fibrillation, smoking, total cholesterol, diabetes, body mass index and systolic blood pressure).
ESVEA = excessive supraventricular ectopic activity.

The risk of stroke associated with ESVEA was greater in patients >65 years of age (Table 4) than in patients ≤65 years of age. The Kaplan-Meier survival function of the 2 groups is depicted in Figure 2.

VARIABILITY OF ATRIAL ECTOPY. ESVEA was classified as ≥30 PACs/h, and we assessed the day-to-day variability of having ≥30 PACs/h. Recordings for each individual were compared for 2 different days against the 48-h monitoring period. This resulted in kappa values for having ≥30 PACs/h of 0.90 (95% CI: 0.83 to 0.98) and 0.89 (95% CI: 0.82 to 0.97), respectively. Thus, if a person has excessive PACs in a 24-h examination, there is a very high probability of having the same finding on a following day.

SENSITIVITY ANALYSIS. A nonlinear association between number and runs of PACs with stroke was observed (Figure 3). In univariate analysis, a dichotomized variable for top decile for PACs/hour and runs of PACs each correlated with stroke (HR: 2.24; 95% CI: 1.23 to 4.09; and HR: 2.82; 95% CI: 1.44 to 5.5; respectively). When adjusting for conventional risk factors (age, sex, smoking, total cholesterol, diabetes, body mass index, and systolic blood pressure), runs of PAC remained associated with stroke (HR: 2.26; 95% CI: 1.1 to 4.64), whereas PACs/hour did not (HR: 1.60; 95% CI: 0.86 to 3.02). In a subanalysis, we tested subjects with runs ranging from 20 to 50 PACs to determine whether shorter runs lasting <0.5 min had an impact on the risk of stroke. Both in univariate analysis (HR: 2.61; 95% CI: 1.19 to 5.70) and after adjusting for gender and age (HR: 2.43; 95% CI: 1.11 to 5.33), the results remained significant.

The positive and negative predictive values of ESVEA in relation to ischemic stroke were 21.2% and 91%, respectively. To assess whether ESVEA adds prognostic value to the Framingham Stroke Risk Score, we calculated the Framingham Stroke Risk Score of all subjects. With ischemic stroke as the endpoint, the HR for each increase of 1 point was 1.20

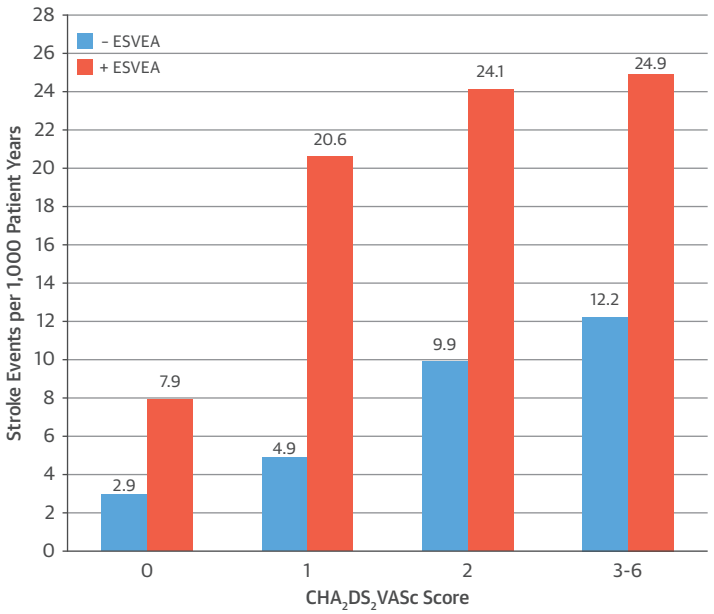
(95% CI: 1.14 to 1.28; p < 0.000). With entrance of ESVEA to the model, ESVEA maintained prognostic value for ischemic stroke (HR: 2.10; 95% CI: 1.25 to 3.56; p = 0.005). A likelihood ratio test including ESVEA showed that the model improved significantly (likelihood ratio chi-square = 6.88; p = 0.0087).

DISCUSSION

MAJOR FINDINGS. The principal finding of this study is that in middle-aged and older study subjects with no apparent heart disease, ESVEA is associated with an increased risk of ischemic stroke. The study also shows a strong correlation between ESVEA and ischemic stroke beyond AF. Both in censoring analysis and when modeling AF as a time-varying exposure, the results were significantly associated with ischemic stroke in fully adjusted models. In a competing risk analysis with death and AF as competing events, the association between ESVEA and ischemic stroke attenuated to insignificant. In all likelihood, this finding demonstrates that subjects with ESVEA, compared with those without, have a greater risk of dying or developing AF before they have a stroke. However, 82% of the subjects with ESVEA did not develop clinical AF during the follow-up of 15 years, and only a minority (14.3%) among the subjects with ESVEA who had a stroke also had a diagnosis of incident AF. The absolute risk of stroke in subjects with ESVEA and a CHA_2DS_2-VASc score ≥2 was 2.4% per year, which is equivalent to patients with AF and a CHA_2DS_2-VASc score of 2 (20,21). This is classified as a high risk, and it normally warrants anticoagulation in patients with AF. Addition of ESVEA to the Framingham Stroke Risk Score showed that ESVEA maintained prognostic value. Thus ESVEA may be considered a risk factor for ischemic stroke.

VALUE OF ESVEA AS A NOVEL METHOD TO PREDICT STROKE. Traditionally, the only arrhythmias that are viewed as causing ischemic stroke are manifest AF or atrial flutter (22). This study suggests that other atrial electric instabilities, such as ESVEA and even short runs of 20 to 50 PACs, can account for some proportion of cryptogenic strokes. Earlier research investigating the causes of unexplained ischemic stroke supports this hypothesis (23,24). Kamel et al. (23) demonstrated an independent association between paroxysmal supraventricular tachycardia and subsequent ischemic stroke (HR: 2.10; 95% CI: 1.69 to 2.62) in a large, demographically diverse cohort with no earlier diagnosis of AF. In a similar fashion, a study by Healey et al. (24) showed a link between subclinical AF, defined as episodes of atrial rate >190 beats/min for >6 min, and the risk of ischemic stroke in patients without clinical AF and no earlier events of stroke (HR: 2.50; 95% CI: 1.28 to 4.89). In another study, Ofoma et al. (25) reported that a finding of PAC and premature ventricular contraction on a 2-min ECG strip was associated with an increased risk of ischemic stroke. However, the associations attenuated into insignificant after adjustment for coexisting risk factors. The inconsistencies between this study and ours may reflect

FIGURE 1 Incidence of Stroke per 1,000 Patient-Years According to ESVEA and CHA_2DS_2-VASc score



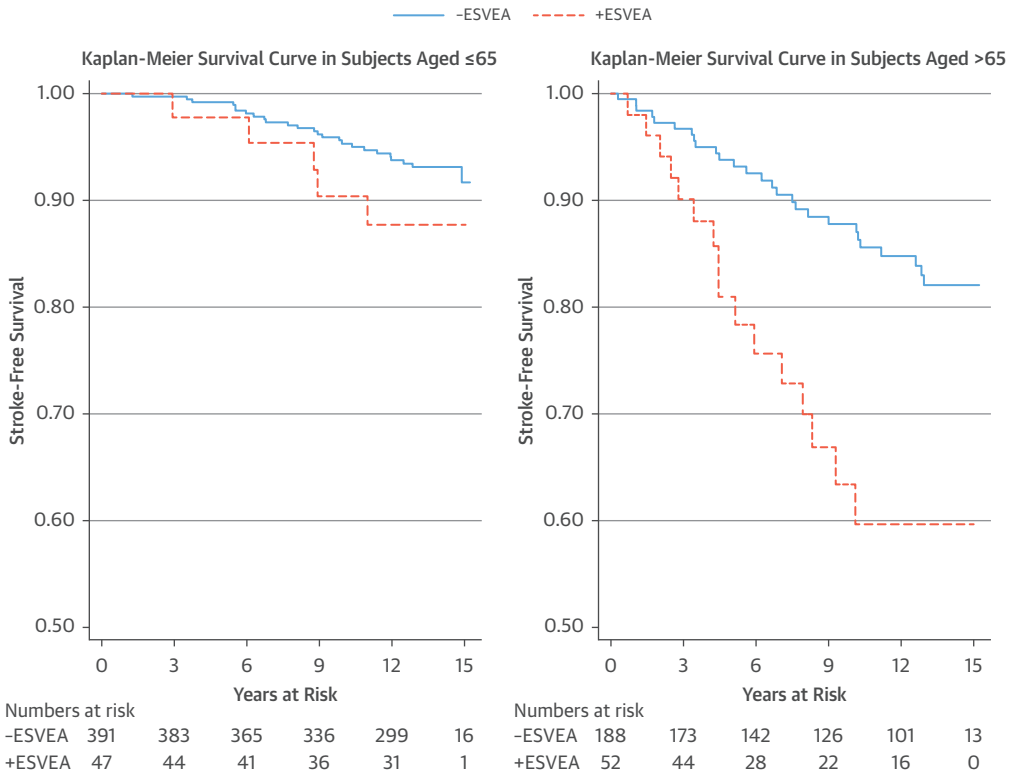
A stepwise increase in the rates of stroke was observed with increasing CHA_2DS_2-VASc (congestive heart failure, hypertension, age 75 years or older, diabetes mellitus, previous stroke or transient ischemic attack, vascular disease, age 65 to 74 years, female) score and a significantly higher risk in the patients with excessive supraventricular ectopic activity (ESVEA) (p = 0.0002).

TABLE 4 Number of Strokes per 1,000 Person-Years in Relation to ESVEA and Age Groups

Age Group, yrs	Presence (+) or Absence (–) of ESVEA	n	Stroke, n (%)*	Time at Risk (yrs)	Strokes/1,000 Person-Yrs (95% CI)	p Value†
≤65	– ESVEA	391	25 (6.4)	5,045	5.0 (3.3–7.3)	Reference
n = 438	+ ESVEA	47	5 (10.6)	559	8.9 (3.7–21.5)	0.2086
>65	– ESVEA	188	27 (14.4%)	1,978	13.6 (9.4–19.9)	Reference
n = 240	+ ESVEA	52	16 (30.8%)	415	38.5 (23.6–62.9)	0.0007

*Indicates % of number in the row. †Log-rank test for equality of survivor function.
CI = confidence interval; ESVEA = excessive supraventricular ectopic activity.

FIGURE 2 Kaplan-Meier Survival Estimate of Stroke-Free Survival Stratified on Age-Groups and ESVEA



The risk of stroke associated with excessive supraventricular ectopic activity (ESVEA) was greater in patients >65 years of age ($p = 0.0007$), but not in patients ≤65 years of age ($p = 0.2086$).

the different populations studied or the method of detection of PAC or premature ventricular contraction. The identification of subjects with increased ectopy on the basis of a 2-min ECG may have some limitations compared with 48 h of continuous ECG recording.

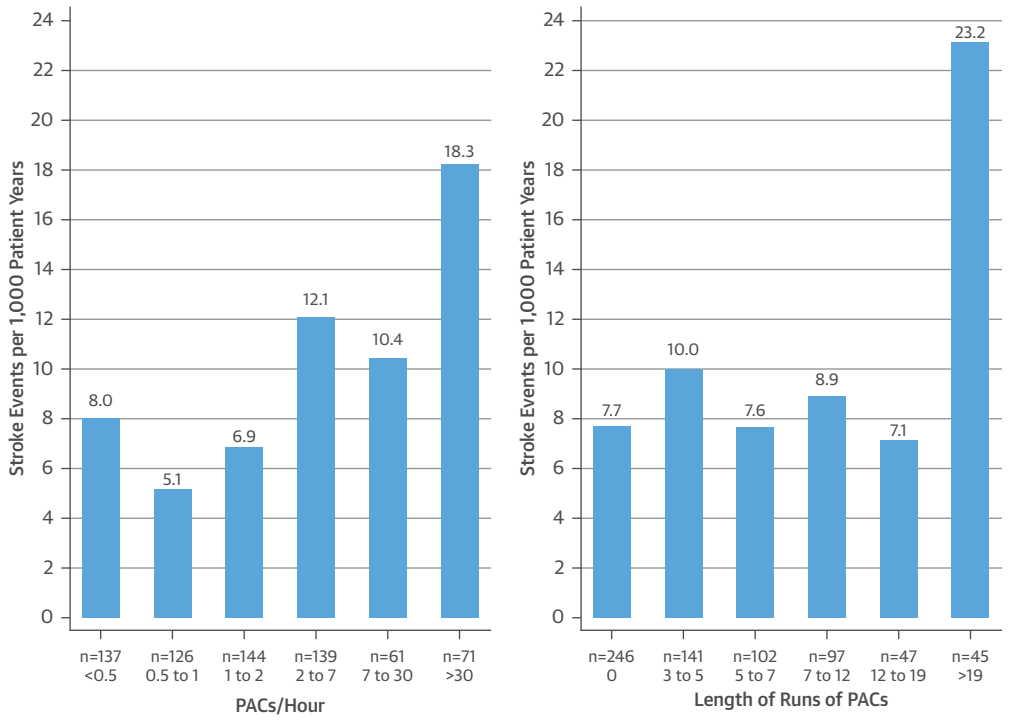
The possible pathophysiological mechanism by which excessive AE may contribute to increase the risk of ischemic stroke is unclear. The most likely explanation is that increased ectopic activity precedes undiagnosed incident AF and thus enhances the possibility of cardioembolism and stroke. Kochhäuser et al. (26) demonstrated that increased ectopic activity (>14.1/h) and supraventricular runs (>0.2 h) in patients with cryptogenic stroke are associated with a high risk of future AF (relative risk: 4.0; 95% CI: 1.1 to 14.6). A similar study by Wallmann et al. (27) showed that frequent PAC (>70/24 h) represents a risk factor, independent of traditional risk factors, for paroxysmal AF (odds ratio: 6.6; 95% CI: 1.6 to 28.2) in patients with recently diagnosed ischemic stroke.

Another possibility could be that increased AE is a marker of more severe hypertension, diabetes, physical inactivity, or lipid metabolism abnormality (28), thus signifying an increased vascular risk profile and an increased probability of stroke in these subjects. In that case, ESVEA may identify patients with more target organ damage.

A third and hypothetical mechanism could be that interactions between coexisting risk factors such as hypertension and smoking, in addition to increased number and runs of PACs, may lead to dilation of the left atrium, stasis in the left atrial appendage, fibrosis, and endothelial dysfunction, eventually resulting in a hypercoagulable state comparable to that present in AF (29–32). The different hypotheses are not mutually exclusive and may coexist in patients (**Central Illustration**).

DETECTION OF AF. AF is a well-established risk factor for ischemic stroke and thromboembolisms. However, a shortcoming of the short-term ECG-recording

FIGURE 3 Incidence of Stroke per 1,000 Patient-Years in Relation to Average Hourly PACs and Length of Runs of PACs



A nonlinear association between number and runs of premature atrial contractions (PACs) with stroke was observed in these patients.

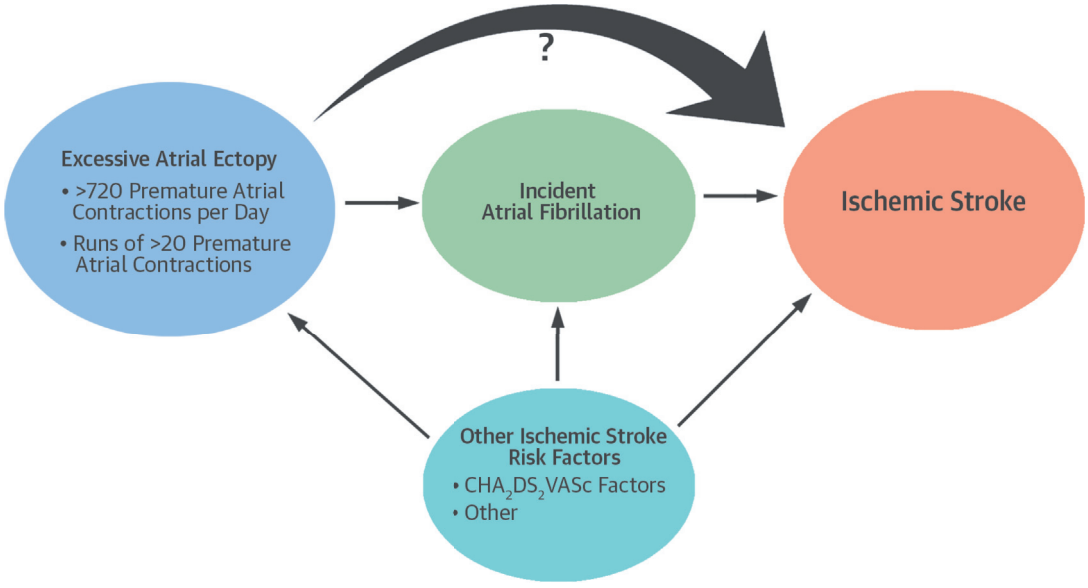
for detecting AF is the rarity of episodes. Recent prospective studies in search of cardiovascular causes behind cryptogenic stroke have demonstrated a better diagnostic yield of AF with prolonged ECG recording. A study by Gladstone et al. (8) used a 30-day event-triggered loop recorder and had a detection rate of 16.1% (3.2% in the control group). A comparable study by Sanna et al. (5) used an insertable cardiac monitor with the primary endpoint being detection of AF within 6 months, and it had a detection rate of 8.9% (1.4% in control group). Both studies were using control groups with conventional follow-up including Holter monitoring (5,8). The increased detection rate with prolonged ECG monitoring is reflected in the latest guideline from the American Stroke Association. This organization recommends rhythm monitoring for up to 30 days within 6 months of an index ischemic stroke or transient ischemic attack compared with the previous recommendation of 24 h or more (22,33). However, the extensive diagnostics are time consuming for both patients and doctors, and many of these patients may have ESVEA and be considered at risk from the outset.

The advantage of using ESVEA as a novel method to predict stroke would be that ESVEA is more frequent than episodes of AF. We have shown excellent day-to-day reproducibility for detecting ESVEA, and ESVEA may therefore serve as an early and more consistent finding as compared with rare episodes of AF. Future studies are needed to evaluate whether intensive risk factor modification in these patients could improve the outcome, as shown in patients with AF and paroxysmal AF (34).

STUDY LIMITATIONS. All causation between PAC and ischemic stroke has not been documented. Subjects with manifest or previous heart disease were excluded from this study, and we cannot dismiss the possibility that ESVEA is an epiphenomenon of undetected heart diseases, which increase the risk of stroke independently of the ectopic activity.

Although we adjust for several known covariates associated with ischemic stroke in the regression

CENTRAL ILLUSTRATION **Excessive Atrial Ectopy and Other Risk Factors in Relation to Ischemic Stroke**



Larsen, B.S. et al. J Am Coll Cardiol. 2015; 66(3):232–41.

Excessive atrial ectopy and short atrial runs are associated with an increased risk of ischemic stroke beyond atrial fibrillation. However, the exact mechanism is not known and may be caused by undiscovered incident atrial fibrillation or an increased vascular risk profile. CHA_2DS_2-VASc = congestive heart failure, hypertension, age 75 years or older, diabetes mellitus, previous stroke or transient ischemic attack, vascular disease, age 65 to 74 years, female.

analyses, residual confounding may have influenced the results. Because echocardiography and carotid ultrasound examinations were not performed in these subjects, we could not account for structural cardiac abnormalities and possible carotid plaques. However, NT-proBNP values were almost in the normal range in subjects with ESVEA, and analyses adjusting for this factor did not change the results significantly. In addition, other unknown confounding factors (e.g., sleep apnea) could trigger paroxysmal AF and stroke in some cases in subjects with risk factors. Hence some degree of residual confounding cannot be excluded, especially with regard to the composite endpoint of stroke and death.

The follow-up period of up to 15 years increases the number of events and thus increases the power to detect associations. Nevertheless, because risk factors change over the course of a decade, a direct cause and effect relationship is difficult to demonstrate.

In regression analysis using PACs and runs of PACs as continuous variables, we could not establish a "dose-response" association. We previously reported linear associations between PACs or runs of PACs and AF (11), but it seems that PACs and runs must be more extreme to constitute a risk for stroke. However, study subjects in the top decile carried a worse prognosis in both hourly PACs and runs of PACs. Although the definition of ESVEA was made on the basis of previously published reports, this arbitrarily defined cutoff point needs to prove its value in other populations.

CONCLUSIONS

In this middle-aged and older population, ESVEA was associated with an increased risk of ischemic stroke beyond manifest AF. Stroke was more often the first clinical presentation, rather than incident AF. ESVEA is a clinically stable and consistent finding that seems to confer a stroke risk comparable to that of AF.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: PACs are often asymptomatic and considered benign, but frequent or longer runs of PACs (other than AF or atrial flutter) are associated with an increased risk of ischemic stroke in middle-aged and older patients.

TRANSLATIONAL OUTLOOK: More research is needed to determine whether the risk of stroke in patients with high-grade AE is related to thrombogenic atrial disease or later development of AF, and randomized trials should assess whether antithrombotic treatments or other risk factor modifications reduce the risk of ischemic stroke in patients with atrial ectopy other than AF or atrial flutter.

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